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TRANSMITTAL OF APPEAL BRIEF

Docket No.
C2432.0037/P001

In re Application of: Lars Wiklund et al.

Application No.	Filing Date	Examiner	Group Art Unit
09/773,394-Conf. #5538	January 31, 2001	M. Bahar	1617

Invention: PRESERVATION OF BODILY PROTEIN

TO THE COMMISSIONER OF PATENTS:

Transmitted herewith in triplicate is the Appeal Brief in this application, with respect to the Notice of Appeal filed: December 5, 2003 .

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Docket No.: C2432.0037/P001

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:

Lars Wiklund et al.

Application No.: 09/773,394 Confirmation No.: 5538

Filed: January 31, 2001 Art Unit: 1617

For: PRESERVATION OF BODILY PROTEIN Examiner: M. Bahar

APPELLANT'S BRIEF

MS Appeal Brief - Patents
Commissioner for Patents
P.O. Box 1450
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This appeal brief is submitted in furtherance of the Notice of Appeal, filed in this case on December 5, 2003.

This brief contains items under the following headings as required by 37 C.F.R. § 1.192 and M.P.E.P. § 1206:

I. Real Party In Interest
II Related Appeals and Interferences
III. Status of Claims
IV. Status of Amendments
V. Summary of Invention
VI. Issues
VII. Grouping of Claims
VIII. Arguments
IX. Claims Involved in the Appeal
Appendix A Claims

I. REAL PARTY IN INTEREST

The real party in interest for this appeal is Pharmalink AB

II. RELATED APPEALS AND INTERFERENCES

There are no other appeals or interferences known to the Appellants, the Appellants' legal representative, or assignee, which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

III. STATUS OF CLAIMS

Claims 2 and 4-21 are currently pending and are the subject of this Appeal.

Claim 3 was previously cancelled.

IV. STATUS OF AMENDMENTS

There are no un-entered Amendments in this case.

V. SUMMARY OF INVENTION

Glutamine, one of the predominant amino acids in the body, is mainly utilized as an energy source and nitrogen carrier. During post-operative and posttraumatic catabolism, its availability is decreased resulting in depletion of skeletal muscle glutamine and, with continued utilization of glutamine by the intestine, to low blood glutamine levels.

The administration of glutamine to a patient in the state of glutamine depletion is less than a direct way of coping with the deficiency since glutamine is poorly soluble in water and cannot be sterilized by autoclavation. A more direct way of preserving or raising blood glutamine levels is highly desirable.

Alpha-ketoglutarate (α-KG), the biologic precursor of glutamine, has been tried in human internal and parental nutrition but in clinical studies, the recorded effect have been small and judged to be of minor importance.

Ammonium has been occasionally administered to patients in the form of a pharmacologically acceptable salt such as a chloride, despite the fact that it is considered neurotoxin in that high concentrations are known to be neurotoxic. It is known to cause metabolic acidosis. Its recommended pharmaceutical uses are few.

The present invention provides a method of preserving body protein stored in a catabolic patient by the concomitant administration of a pair of pharmaceutical agents in amounts effective to preserve skeletal muscle. The first agent contains alpha-ketoglutarate (α-KG) and/or alpha-ketoglutaric acid (α-KA) and is devoid of ammonium. The second agent contains ammonium but is devoid of alpha-ketoglutarate and alpha-ketoglutaric acid.

VI. ISSUES

The sole issue in this case is whether the invention set forth in the pending claims is obvious under the provisions of 35 U.S.C. § 103(a) over Veech (U.S. 5,719,119) and Vinnars (U.S. 5,310,768).

A rejection of the claims under 35 U.S.C. § 112, first paragraph, set forth in the final rejection was withdrawn in an Advisory Action.

VII. GROUPING OF CLAIMS

The claims do not stand or fall together.

In Section VIII below, Applicant has included arguments supporting the separate patentability of each claim group as required by M.P.E.P. § 1206.

VIII. ARGUMENTS

One of the predominant amino acids in the body, glutamine, is mainly utilized as an energy source and nitrogen carrier. Its availability is decreased during post-operative and posttraumatic catabolism, resulting in depletion of skeletal muscle glutamine and, with continued utilization of glutamine by the intestine, to low blood glutamine levels. While administration of glutamine to a patient in the state of glutamine depletion would appear to be desirable, it is less than a direct way of coping with the deficiency since glutamine is poorly soluble in water and cannot be sterilized

by autoclavation. See, e.g., Vinnars at column 2. lines 30-40. A more direct way of preserving or raising blood glutamine levels is highly desirable.

The present invention provides a method of preserving body protein stored in a catabolic patient by the concomitant administration of a pair of pharmaceutical agents in amounts effective to preserve skeletal muscle. The first agent contains alpha-ketoglutarate (α-KG) and/or alpha-ketoglutaric acid (α-KA) and is devoid of ammonium. The second agent contains ammonium but is devoid of alpha-ketoglutarate and alpha-ketoglutaric acid.

Alpha-ketoglutarate (α-KG) is a biologic precursor of glutamine. Its use has been investigated in human internal and parental nutrition but in clinical studies, the recorded effects have been small and judged to be of minor importance. As noted infra, a recent study concludes there is no valid rationale for its use in an enteral compostion.

Ammonium has been occasionally administered to patients in the form of a pharmacologically acceptable salt such as a chloride, despite the fact that it is considered a neurotoxin in that high concentrations are known to be neurotoxic. It causes metabolic acidosis. The recommended pharmaceutical uses of ammonium are few.

Nevertheless, the inventors found out that concomitant administration was advantageous. In another surprising finding, the inventors also found that infusion

increased arterial glutamine concentration in a dose dependent fashion when the ammonium load was increased and the dose of α-KG was kept constant but not when the α-KG load was increased and the dose of ammonium was kept constant. Data establishing this surprising finding is presented in the application.

The primary reference relied on by the Examiner, Veech, relates to a parenteral nutritional aqueous solution which contains one or more of 20 metabolizable nitrogen containing compounds, one or more of 6 carboxylic metabolite anions and one or more of 5 cations. Among the 6 carboxylic metabolite anions is alpha-ketoglutarate and among the 5 cations is ammonium. The patent sets forth reasons for each of these materials to be present. It teaches that the presence of the metabolite anions in the composition of the Veech invention exert a desirable alkalinizing action which avoids metabolic acidosis. (col. 13, lines 62-65). The patent also points out that normal plasma contains concentrations of ammonium, α-KG and glutamate which is equivalent to the free mitochondrial free NAD/NADH ratio and if fluids are given which do not contain these substances, the cells alter their metabolism to realize that ratio. Accordingly, the presence of both α-KG and ammonium in the amino acid solution containing glutamate controls the redox state of the mitochondria. (col.13, line 66 to col. 14, line 20) Also, the presence of both ketoglutarate/glutamine at concentrations around the physiologically normal avoids the use of free ammonia, but generates ammonia and the production of intracellular glutamate. (col. 14, lines21-24) Thus, the reference teaches the presence of

both ammonium and α-KG in the same solution in order to control the redox state. Col. 13, line 66 et. seq. Further, the presence of both is designed to make the solution electrically neutral. (Col. 18, lines 51 et. seq.).

If the metabolite anion α-KG is present in the composition of the Veech for the purpose of avoiding metabolic acidosis, why would one employ a separate administration of a material such as ammonium which is known to cause metabolic acidosis when so administrated? There is no reason.

If the absence of ammonium or α-KG in a single fluid causes cells to alter their metabolism, why would one intentionally omit one? There is no reason.

If the presence of both α-KG and ammonium in the amino acid solution containing glutamate controls the redox state of the mitochondria, why would one be omitted? There is no reason.

If Veech teaches his combination avoids the use of free ammonia, why would one administer ammonium separately? There is no reason.

It will be appreciated from the foregoing, that the Veech reference teaches solution which contains a combination of alpha-ketoglutarate and ammonium in all instances and further provides reasons why both should be present. There is no reason or motivation to separate them.

Vinnars teaches the addition of alpha-ketoglutarate to a conventional amino acid solution but does not mention ammonium. Since this teaching is also found in Veech, the Vinnars reference does not add anything of substance vis-à-vis the instant rejection. Apparently, the only additional of disclosure in this reference on which reliance is being had is the fact that the concentration administered of the alpha-ketoglutarate should be at least 0.1g/kg body weight/day.

Vinnars points out that that glutamine reduction was not affected by enteral or parenteral nutritional support before the invention there described. He found that alpha-ketoglutarate worked in certain compositions even though ornithine-alpha-ketoglutarate had a limited effect and was not known whether there would be any clinical advantage (column 2, lines 11-20). A recent paper by Wiren (of record) describes a study to evaluate the feasibility of using α-ketoglutarate enrichment in enteral feeding and the effect on protein metabolism after major surgery. The authors concluded that enrichment of a whole protein-based formula with α-ketoglutarate did not improve protein metabolism or decrease muscle catabolism after major abdominal surgery. See e.g., the summary on page 725 and the concluding paragraph in the paper. The findings of the study were sufficiently important to elicit an editorial opinion (also of record). Note that the concluding sentence by Dr. Cynober in that opinion states that based on both the Wiren study and the available literature, there is no rationale for

providing an α-ketoglutarate enriched enteral diet in post-operative patients. These teachings indicate that predictability in this art is limited.

The combination of references advanced in this rejection does not teach or suggest the use of two separate compositions, one containing alpha-ketoglutarate and/or alpha-ketoglutaric acid and the other containing ammonia, when neither of these compositions contain the other substance. The Veech reference discloses them but calls for a single solution containing both α-KG and ammonium, provides reasons both should be present and does not suggest separating them.

The Office Action seeks to overcome this basic deficiency by asserting that one skilled in the art would have been motivated to separate the two materials. The reason given is that both are known to be useful in methods of treating post-operative/post-traumatic patients and normalizing/preserving skeletal muscle glutamine/nitrogen content. This attempted hindsight justification should be rejected for at least two reasons. First, there is no factual basis for the assertion that ammonium alone is known to be useful in such methods. The rejection does not identify where such disclosure is found nor has any such teaching been found in the references applied or elsewhere in the instant record. Veech does teach the use of ammonium but only within the same aqueous solution as the alpha-ketoglutarate and there is no implication it can be used separately. Quite the contrary, Veech provides a variety of reasons why the ammonium should be in the same composition as the α-KG and this is a second reason

for rejecting the alleged motivation. If the presence of a material in a composition has been taught to provide advantages, then there must be a good reason existent before one skilled in the art would separate that material from the composition. The rejection does not even hypothesize such a reason.

In the case of *In re Freed*, 165 USPQ 570 (1970), the CCPA had occasion to observe that ". . . it seems more logical and reasonable to infer that one teaching a chemical reaction process would set out the least number of reactions thought to be necessary to accomplish the desired objectives." Applying similar logic, its seems more logical that one teaching a composition would want all of the components in a single composition so that the least number of compositions need be administered. Separating the components in the absence of a reason to do so is illogical.

The Office Action also attempts to provide motivation by asserting that "combining two agents which are known to be useful . . . into a single composition useful for the same purposes is prima facie obvious." (Final Rejection, page 4). But the invention does not involve combining two agents into a single composition. Two separate compositions are used. Once again, it is respectfully submitted that one would not separate α-KG and ammonium in the absence of a reason and no reason has even been hypothesized.

The foregoing discussion has focused on claim 1 on appeal. There are additional reasons why groups of the dependent claims are patentable over this art.

Claims 2-4 and 21 recited the duration of administration. Claim 20 (on which claim 21 is dependent) specifies that ammonium chloride is administered. There is no basis in the art to contend these claims are obvious.

Claim 6 specifies that the administrations are by infusion. Claim 7-10 and 15-19 specify rates of infusion. Beyond the fact that the references do not teach or suggest two separate infusions, there is no factual basis for selecting any rate of infusion. The Office Action attempts to overcome this deficiency by asserting that the determination of amounts is mere optimization. In reality, this is merely a suggestion that it would be obvious to try various administration rates. It is well established that an obvious to try standard does not meet the requirements of §103.

Claims 11 - 14 recite that the infusion of the ammonium is increased over the period of administration. The art does not suggest changing the rate of administration of any material during the administration period for any reason. As noted earlier, changing the ammonium rate provides advantages which are not realized when the rate of the α-KG is increased. Nothing in the art suggests the ammonium rate should be changed.

For all the reasons set forth above, it is respectfully submitted that the rejection under §103 should be reversed.

IX. CLAIMS INVOLVED IN THE APPEAL

A copy of the claims involved in the present appeal is attached hereto as Appendix A.

Dated: April 2, 2004

Respectfully submitted,

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APPENDIX A

1. A method of preserving bodily protein stores in a catabolic patient, comprising the concomitant administration of a pair of pharmaceutical agents consisting essentially of (a) a first composition containing at least one of α-ketoglutarate and α-ketoglutaric acid and being devoid of ammonium, and (b) a second composition containing ammonium and being devoid of a α-ketoglutarate and α-ketoglutaric acid, the amounts of the pair being effective to preserve skeletal muscle.

2. The method of claim 1, wherein the administration of (a) or (b) or both lasts for more than one hour.

4. The method of claim 2, wherein the concomitant administration lasts for more than 6 hours but less than 36 hours.

5. The method of claim 1, wherein the administration is to a patient having undergone trauma or surgery and the administration is intermittent or continuous for at least three days of the posttraumatic/postoperative period during which the patient is in a catabolic state.

6. The method of claim 1, wherein administration is by infusion.

7. The method of claim 6, wherein the amount of infusion administrated of (a) is from 0.02 $\mu mol \cdot kg^{-1} \cdot min^{-1}$ to 30 $\mu mol \cdot kg^{-1} \cdot min^{-1}$.

8. The method of claim 7, wherein the amount of infusion administrated of (a) is from 0.5 $\mu mol \cdot kg^{-1} \cdot min^{-1}$ to 15 $\mu mol \cdot kg^{-1} \cdot min^{-1}$.

9. The method of claim 6, wherein the amount of infusion administrated of NH_4^+ is from 0.5 $\mu mol \cdot kg^{-1} \cdot min^{-1}$ to 20 $\mu mol \cdot kg^{-1} \cdot min^{-1}$.

10. The method of claim 9, wherein the amount of infusion administrated of NH_4^+ is from 1 $\mu mol \cdot kg^{-1} \cdot min^{-1}$ to 10 $\mu mol \cdot kg^{-1} \cdot min^{-1}$.

11. The method of claim 9, wherein the amount of infusion administrated of NH_4^+ is increased over the period of administration.

12. The method of claim 11, wherein the amount of infusion administrated of (a) is from 0.02 $\mu mol \cdot kg^{-1} \cdot min^{-1}$ to 30 $\mu mol \cdot kg^{-1} \cdot min^{-1}$.

13. The method of claim 11, wherein said increase is by a factor of from 1.5 to 8.

14. The method of claim 13, wherein said increase is by a factor of from 2 to 5.

15. A pharmaceutical dosage unit comprising a first pharmaceutical composition comprising at least one of α-ketoglutarate and α-ketoglutaric acid in a pharmaceutically acceptable carrier and being devoid of ammonium, and a second pharmaceutical composition comprising ammonium in a pharmaceutically acceptable carrier and being devoid of α-ketoglutarate and α-ketoglutaric acid, the total amount of the at least one of α-ketoglutarate and α-ketoglutaric acid and the ammonium being effective to preserve skeletal muscle, and wherein the amount administrated of said at least one of α-ketoglutarate and α-ketoglutaric acid is from 0.02 $\mu mol \cdot kg^{-1} \cdot min^{-1}$ to 30 $\mu mol \cdot kg^{-1} \cdot min^{-1}$ and the amount of infusion administrated of NH_4^+ is from 0.5 $\mu mol \cdot kg^{-1} \cdot min^{-1}$ to 20 $\mu mol \cdot kg^{-1} \cdot min^{-1}$.

16. The unit of claim 15, wherein both carriers are an infusion carrier.

17. The unit of claim 15, wherein both carriers are an oral carrier.

18. The unit of claim 15, wherein the α-ketoglutarate is in form of its sodium.

19. The unit of claim 15, wherein ammonium is in form of its chloride.

20. The method of 1, wherein the ammonium is ammonium chloride.

21. The method of claim 20, wherein the administration of (a) or (b) or both lasts for more than one hour.